Cocaine Use and Hypertensive Renal Changes in HIV-Infected Individuals

Derek M. Fine,* Neha Garg,† Mark Haas,‡ M. Hafizur Rahman,*§ Gregory M. Lucas,* Paul J. Scheel,* and Mohamed G. Atta*

Departments of *Medicine and ‡Pathology, Johns Hopkins School of Medicine and the Johns Hopkins Hospital, and §Department of International Health, Division of Health Systems, Johns Hopkins University, Bloomberg School of Public Health, Baltimore, Maryland; and †Department of Medicine, All India Institute of Medical Sciences, New Delhi, India

Background and objectives: Cocaine causes kidney damage, but data linking cocaine use to chronic kidney disease in HIV patients is not described. This study was conducted to evaluate the possible association of cocaine use and histopathologic findings on biopsy in this population.

Design, setting, participants, & measurements: Kidney biopsies that were performed in HIV-infected patients during the course of 11 yr were reviewed. Demographic and clinical data were collected. Hypertensive changes were defined on the basis of the Banff 97 classification. Criteria of both arterial intimal fibrosis and thickening and hyaline arteriolosclerosis were used and graded as absent (0), mild (1), moderate (2), and severe (3). Hypertensive renal changes were considered present when the combined pathology score was ≥2. To minimize confounding, those with hypertension or diabetes were excluded.

Results: Of the 193 HIV patients who underwent kidney biopsy, 53 had no history of hypertension or diabetes with HIV infection. Of those, 29 (55%) had hypertensive renal changes on kidney biopsy. Cocaine use was present in 16 (55%) of 29 with hypertensive renal changes compared with six (25%) of 24 without hypertensive renal changes (odds ratio [OR] 3.7; 95% confidence interval [CI] 1.2 to 11.7). In the adjusted analyses, only age (/yr; OR 1.08; 95% CI 1.00 to 1.16) and cocaine use (OR 3.55; 95% CI 1.04 to 12.14) were significantly associated with hypertensive renal changes on renal biopsy.

Conclusions: Cocaine use is associated with hypertensive renal changes in HIV-infected patients in the absence of hypertension and diabetes.


Lifetime exposure to substance abuse in the general population is 46% (1). Evidence exists linking substance abuse with several renal syndromes (2–5). Nonetheless, no study has assessed effects of cocaine use on the kidney in HIV patients.

Cocaine is an alkaloid compound obtained from the plant Erythroxylon coca, which is purified to a powder form, cocaine hydrochloride, and used intranasally or dissolved in water and injected intravenously (6). A second form, freebase (crack), is produced and smoked when sodium bicarbonate is added and the mixture is heated to remove the hydrochloride moiety (6). When consumed, it acutely causes hypertension by blocking neuronal reuptake of catecholamines and dopamine (7). In addition, because it possesses powerful vasoconstrictor properties, it is capable of causing myocardial infarction, arrhythmia, sudden death, stroke, seizures, and bowel necrosis, among other complications (Table 1) (8–13). Despite its acute effect on BP, long-term cocaine use has not been associated with chronic hypertension in middle-aged black men (14).

A widely recognized effect of cocaine on the kidney is tubular injury caused by rhabdomyolysis (15). Of interest, hypertension may be absent at presentation of these cases. Studies of direct renal vascular effect as a result of cocaine use are limited to reports of severe arteriosclerosis (16,17) and severe narrowing of the intrarenal arteries as a result of intimal fibrosis, a finding that was later confirmed in an autopsy study of cocaine users (18). This study was conducted to evaluate the association of cocaine and vascular renal changes in HIV-infected individuals who did not have a preexisting history of hypertension and who had a kidney biopsy.

Concise Methods

Participants

All HIV-infected individuals who underwent renal biopsy at the Johns Hopkins hospital between February 7, 1995, and May 12, 2006, were retrospectively studied. The Johns Hopkins institutional review board approved the research protocol.

Data on demographics (age, gender, and race), comorbid conditions (diabetes, hypertension, hepatitis B and hepatitis C infection, and substance drug use), medications, and laboratory measurements at time of renal biopsy (serum creatinine, urinary protein excretion by spot urinary protein-to-creatinine ratio or 24-h urine collection, CD4 count, and
Definitions

All biopsies were reviewed by a single pathologist (M.H.), who was blinded to the clinical and substance use status of the patients. Hypertensive changes were defined on the basis of the Banff 97 classification (19). Criteria of both arterial intimal fibrosis and thickening (CV score) and hyaline arteriolosclerosis (AH score) were used and graded as absent (0), mild (1), moderate (2), and severe (3). Hypertensive renal changes (HRC) were considered present when the combined pathology score was ≥2.

History of hypertension was defined on the basis of any documentation in the medical chart of any history of hypertension, any BP ≥140/90, or the use of any antihypertensive medications before the kidney biopsy. Diabetes was defined as any documented history of diabetes or any fasting blood glucose >126 mg/dl before the date of biopsy or by the use of oral hypoglycemic agents or insulin.

Illicit drug or tobacco use was defined as any documented use before the renal biopsy date. This was assessed by review of electronic medical charts for each patient, including outpatient clinic visits (both nephrology and HIV clinic), hospital admissions, and discharge summaries. Specific drugs of interest included the previous use of cocaine, heroin, both cocaine and heroin, or other illicit drug use such as marijuana.

Hepatitis C infection was defined as presence of a hepatitis C antibody and/or hepatitis C RNA by reverse transcription–PCR. Hepatitis B infection was defined by the presence of the hepatitis B surface antigen.

Statistical Analyses

Statistical analyses were performed using Stata Software 9 (Stata Corp., College Station, TX). Descriptive statistics using means, medians, proportions, and confidence intervals (CI) were performed on all variables when appropriate. Both demographic and clinical characteristics of patients were compared between patients with or without HRC on renal biopsy. The mean values between groups were compared using t test for continuous variables and χ² test for discrete data. Clinical characteristics were analyzed at the time of renal biopsy. Odds ratios (OR) were obtained from univariate and multivariate models using stepwise logistic regression model to ascertain independent predictors that were associated with the presence of HRC on renal biopsy. Absolute P values and 95% CI for difference between the groups were reported, when appropriate. For all analyses, a type I error rate of 0.05 was used.

Results

Of 193 HIV-infected patients who underwent kidney biopsy, 53 (27.5%) had no history of diabetes or hypertension and were included in the analysis. Table 2 shows the baseline character-
Table 3. Predictors of HRC on kidney biopsy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HRC on Biopsy Present (n = 29)</th>
<th>Absent (n = 24)</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD [range])</td>
<td>43.6 ± 1.8 (27 to 68)</td>
<td>37.9 ± 1.5 (26 to 57)</td>
<td>1.08 (1 to 1.2; per yr)</td>
<td>0.03</td>
</tr>
<tr>
<td>Female gender (n [%])</td>
<td>10 (34.5)</td>
<td>9 (37.5)</td>
<td>0.9 (0.3 to 2.7)</td>
<td>0.80</td>
</tr>
<tr>
<td>Black ethnicity (n [%])</td>
<td>25 (86)</td>
<td>20 (83)</td>
<td>1.3 (0.3 to 5.2)</td>
<td>0.80</td>
</tr>
<tr>
<td>eGFR (ml/min per 1.73 m²; mean ± SD)</td>
<td>48.1 ± 6.7</td>
<td>37.4 ± 11.0</td>
<td>1.00 (0.99 to 1.01)</td>
<td>0.45</td>
</tr>
<tr>
<td>Illicit drug use (n [%])</td>
<td>20 (69)</td>
<td>10 (42)</td>
<td>3.1 (1.0 to 9.5)</td>
<td>0.05</td>
</tr>
<tr>
<td>Cocaine use (n [%])</td>
<td>16 (55)</td>
<td>6 (25)</td>
<td>3.7 (1.2 to 11.7)</td>
<td>0.03</td>
</tr>
<tr>
<td>Heroin (n [%])</td>
<td>18 (62)</td>
<td>8 (33)</td>
<td>2.7 (0.9 to 8.2)</td>
<td>0.07</td>
</tr>
<tr>
<td>Combined cocaine and heroin use (n [%])</td>
<td>14 (48)</td>
<td>5 (24)</td>
<td>4.30 (1.06 to 11.60)</td>
<td>0.04</td>
</tr>
<tr>
<td>Tobacco use (n [%])</td>
<td>17 (58)</td>
<td>12 (50)</td>
<td>1.4 (0.5 to 4.2)</td>
<td>0.50</td>
</tr>
<tr>
<td>Hepatitis B history (n [%])</td>
<td>1 (3)</td>
<td>2 (8)</td>
<td>0.4 (0.0 to 3.2)</td>
<td>0.40</td>
</tr>
<tr>
<td>Hepatitis C history (n [%])</td>
<td>16 (55)</td>
<td>11 (45)</td>
<td>1.5 (0.5 to 4.3)</td>
<td>0.50</td>
</tr>
<tr>
<td>HIVAN (n [%])</td>
<td>3 (10)</td>
<td>3 (13)</td>
<td>0.8 (0.2 to 3.9)</td>
<td>0.80</td>
</tr>
</tbody>
</table>

*CI, confidence interval; eGFR, estimated GFR; OR, odds ratio.

Table 4. Regression model of predictors of HRC on kidney biopsy

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.1</td>
<td>1.00 to 1.16</td>
<td>0.04</td>
</tr>
<tr>
<td>Cocaine</td>
<td>3.6</td>
<td>1.04 to 12.10</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Discussion

Our study demonstrates a high prevalence of cocaine use (46.1%) in our cohort and its strong association with HRC on renal biopsy in the absence of hypertension or diabetes (OR 3.6; P = 0.04). The study also suggests that the renal impact of cocaine is independent of hypertension. HRC were also significantly associated with older age (OR 1.1; P = 0.04). Substance abuse is common, involving a lifetime exposure of 46% in the general population (1). Reports (20) indicate that in some areas of the United States, the percentage of cocaine addicts among young people is as high as 20%. By 1997, 25% of the population reported using illicit drugs at some point in their life and 10% within the past year (4). In a university population in the United States, 6% were found to be cocaine users as documented by hair analysis (21). The much higher prevalence of substance and cocaine use in our study reflects the high prevalence of drug use in urban HIV clinics.
These results suggest that the HRC on renal biopsy are associated with cocaine use, independent of other factors. Studies of acute renal complications of cocaine use have been limited to reports of acute tubular damage as a result of rhabdomyolysis, which remains the most common form of cocaine-induced renal pathology. Acute renal failure in this setting may result from myoglobinuria (15,22) or vasoconstriction (23). Less known renal complications as a result of cocaine use include renal infarction (24) and atherosclerosis of kidney arterioles (16–18). Few studies have been done on the vascular damage that is induced by cocaine in kidney confirmed by biopsies. Di Paolo et al. (18) noted that cocaine may be associated with extensive renal vascular injury that in turn induces tubular and interstitial damage. In their autopsy study, kidneys that were obtained from 40 cocaine users were compared with kidneys from victims of automobile accidents who were not known to have used cocaine. Semiquantitative analysis showed that the ratio of hyalinized to normal glomeruli was significantly increased in cocaine users compared with nonusers. The increases in the dimensions of arterial vessels such as lumen circumference, intima circumference, media circumference, media and intima area, and media thickness were also highly significant (18). Three types of alterations to blood vessels have been postulated to cause renal ischemia in cocaine addicts: Hyperplasia of tunica intima, atherosclerotic lesions, and vascular spasm. Many experimental and autopsy studies (25–28) confirm that cocaine also has pronounced atherogenic activity. One in vitro study (29) suggested that cocaine increases the predisposition to atherosclerosis by enhancing the permeability of the vascular endothelium and thereby the diffusion of atherogenic lipoproteins into the intima. Furthermore, cocaine has been associated with accelerated and malignant hypertension as well as with hastening the progression of hypertensive nephrosclerosis to ESRD (30,31), although confirmation by renal biopsy was not attained. The mechanism by which cocaine use may cause HRC in the studied patients is unclear, although the atherogenic activity of the drug may be implicated. It is possible that cocaine use induces subclinical atherosclerosis that ultimately results in pathologic HRC with its continuous use.

Cardiac complications have been extensively studied among cocaine addicts (32–35). Acute hypertension is a widely known manifestation of cocaine use (9,13,30). In contrast, the association of cocaine use and chronic hypertension has been controversial. In a large study by Brecklin et al. (14), there was no association of cocaine use and chronic hypertension or the development of microalbuminuria in black cocaine users compared with a matched control group of the Third National Health and Nutrition Examination Survey (NHANES III). The Coronary Artery Risk Development in Young Adults (CARDIA) study (36) also demonstrated stable BP over the duration of the study; however, Norris et al. (37) demonstrated that the incidence of black individuals’ developing hypertensive ESRD is increasing and that 44% of these patients have a history of substance abuse, as opposed to 5% having diabetes and 11% with other causes of renal disease. A history of cocaine use was associated with the diagnosis of hypertension-related ESRD in 49 (89%) of 55 cocaine users as compared with 64 (46.4%) of 138 of nonusers (37). It has been postulated that the use of cocaine results in a vicious circle of hastened progression to renal failure by exacerbating hypertension and possibly by causing sustained intrarenal vasoconstriction (30).

Lai et al. (38) postulated in an observational study that HIV infection or cocaine use may independently contribute to early subclinical atherosclerotic cardiovascular disease, and one could argue that uncontrolled HIV itself may induce hypertension-like changes in the kidney in the absence of hypertension; however, we found no association between the diagnosis of HIV-associated nephropathy, a major cause of kidney disease in a predominantly uncontrolled HIV setting, and those with or without HRC. Highly active antiretroviral therapy has been linked to hypertension in a few but not all studies. In a retrospective analysis by Cattelan et al. (39), a significant increase in both systolic and diastolic BP was noted in HIV-infected patients who were on long-term therapy with indinavir compared with baseline BP before protease inhibitor therapy; however, Jung et al. (40) observed no significant difference between hypertensive and normotensive patients when comparing current as well as total duration of specific antiretroviral drugs or combination regimen. Because we excluded all patients with hypertension in the analysis, it is unlikely that the renal vascular damage observed in our study is linked to highly active antiretroviral therapy.

There was no significant association between heroin use and HRC in our study. Heroin-associated nephropathy, described in the 1970s and 1980s, was linked to FSGS (41,42); however, Cunningham et al. (41,42) found no renal pathologic markers that could differentiate FSGS in heroin users from FSGS in nonusers. Other studies demonstrated that renal findings associated with heroin use were nonspecific and no uniform pattern of renal pathologic change existed (43). Our data support the lack of association between heroin use and renal vascular changes.

Although the association between tobacco use and HRC was not statistically significant, the small sample size may explain our findings. It is has been known that smoking may hasten the progression of renal disease associated with both diabetes and hypertension (44). In hypertensive individuals, smoking is an independent risk factor for development of microalbuminuria. Furthermore, smoking has been associated with the progression of lupus nephritis (45), renal artery stenosis (46), and renal tubular dysfunction (47).

Our study has several limitations. Despite the plausible effects of cocaine on renal vasculature, selection bias cannot be eliminated. Patients in our study were HIV-infected, predominantly black urban individuals; therefore, our findings may not be generalizable to geographically different areas or other racial groups. Also, all patients had preexisting kidney disease, which may have an effect on renal vasculature; however, the spectrum of renal diseases in cocaine and non–cocaine users was similar, and mean estimated GFR at the time of biopsy was not different in patients with and without HRC, suggesting that the HRC on renal biopsy are independent of the underlying renal disease. Given the small sample size of our study, a larger study to
confirm our findings is warranted. Finally, our assessment of illicit substance use activity relied on participant self-report, which may decrease reporting of potentially stigmatizing behaviors; however, although substance use is expected to be generally underreported, that our study is limited to HIV-infected individuals, in whom illicit substance use is often the primary risk factor for contracting HIV infection, suggests that underreporting is less likely. In our cohort, the prevalence of illicit substance use was far higher (57%) than other published reports for different population groups.

Conclusions
Our study is the first, to our knowledge, to associate cocaine use in HIV-infected patients with HRC on renal biopsy. This association was independent of baseline renal function and other comorbid conditions. Current management guidelines do not describe cocaine use as a risk factor for kidney disease (48). On the basis of available literature (6) and supported by the findings of this study, we contend that an assessment of drug use history may be an important factor in determining risk for kidney disease. Co-management of substance use should be an integral part of therapy in this population.

Disclosures
None.

References
1. Types of Illicit Drug Use in Lifetime, Past Year, and Past Month among Persons Aged 12 or Older: Percentages, 2004 and 2005. Available at: http://oas.samhsa.gov/NSDUH/2k5nsduh/tabs/Sect1peTabs1to66.htm#Tab1.1B, accessed June 12, 2007
2. Orth SR: Adverse renal effects of legal and illicit drugs [in German]. Ther Umsch 59: 122–130, 2002